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COMPLETE SPECIFICATION

Encapsulated Emulsions and Processes for Their Preparation

We, THE UPJOHN COMPANY, a corporation organised and existing under the laws of the State of Delaware, United States of America, of 301, Henrietta Street, Kalamazoo, State of Michigan, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed to be particularly described in and by the following statement:—

This invention relates to a process of encapsulation by liquid-liquid phase separation and to products resulting therefrom, and more particularly to a process of coacervation for encapsulating particles consisting of a hydrophilic-liquid-in-oil emulsion and to the products thereof.

As employed herein, the term lipophilic is applied to those surfaces having relatively strong attractive forces for low dielectric constant and non-polar media. The term hydrophilic refers to those surfaces having relatively strong attractive forces for high dielectric constant and polar media.

According to the novel process of this invention, the novel products hereof are prepared by first forming a primary hydrophilic liquid-in-oil emulsion (the oil being a lipophilic liquid) containing an anti-inversion agent in the oil phase to prevent the inversion of the emulsion. This primary emulsion is then dispersed in a coacervating solution comprising a coacervating agent and an aqueous sol of a coacervatice colloid at a temperature above the gel point of the coacervating colloid to produce a double or secondary emulsion, whereupon a coacervate deposits about the particles of the secondary emulsion.

Liquid-liquid phase separation refers to the separation of a solution or a sol of a polymer, or colloid, or combination of polymers into two distinct liquid phases, one designated as the polymer-rich phase and the other the polymer-poor phase. Where the polymer-rich and polymer-poor phases are colloidal sols rather than true solutions, the phenomenon of phase separation is herein designated as coacervation. Thus, a coacervate is a polymer-rich sol which has separated from an original single-phase polymeric dispersion (either a solution or a sol), leaving behind a polymer-poor sol or equilibrium liquid. The coacervate appears initially as a fine dispersion of microscopic droplets of polymer in the equilibrium liquid. When formed in a pure colloidal system, these droplets are essentially homogeneously distributed throughout the system. However, if foreign materials are present in the original dispersion, the coacervate tends to form around these materials. Technically, the term coacervation therefore relates to the process by which the liquid colloidal concentrate or coacervate is formed as a phase entity of the initial sol or solution. In its practical aspect, and as employed herein, coacervation relates to the process by which foreign materials present in the sol when the coacervate is formed are enveloped or encapsulated by the coacervate. Where the coacervate consists of a single colloid, as herein, the process is termed simple coacervation; where more than one colloid is present in the coacervate, the process is called complex coacervation.

Coacervation has long been known as a phenomenon primarily of academic interest, and only in recent years has it been developed in certain limited aspects for commercial utilization. However, even with this renewed interest in the subject, the technique has been successfully described only for the coating of oil droplets per se and of oil droplets containing dissolved or dispersed materials. British Patent Specification 751,600 discloses methods for encapsulating oil droplets by coacervate coatings of the complex and simple types, respectively. Although this

specification describes the formation of coacervates from an oil-in-water emulsion, only the oil phase is actually encapsulated by the coacervate. Prior to the present invention, the encapsulation of an intact emulsion had not been reported by the coacervation technique, and the important advantages of a coacervate-coated emulsion in which either or both the phases thereof contain dissolved or suspended active ingredients have not been heretofore obtainable.

It has now been unexpectedly found, however, that particles of a primary emulsion consisting of a hydrophilic liquid-in-oil emulsion constituting the dispersed phase of a secondary emulsion can be encapsulated by coacervation if the oil phase of the primary emulsion contains a substance, herein designated an anti-inversion agent, capable of preventing the inversion of the hydrophilic liquid-in-oil emulsion to an oil-in-hydrophilic liquid emulsion in the course of coacervation.

It has likewise been found that a further improvement in the efficiency of the coacervation process as applied to hydrophilic liquid-in-oil emulsions and in the properties of the resulting encapsulated products can be realized by the addition of a thickening agent to the hydrophilic liquid phase of the primary emulsion to fix the dissolved or suspended active ingredients therein during coacervation. Additionally, it has been found that the presence of a thickening agent in the aqueous solution of the coacervating agent enhances the integrity of the individual phases of the secondary emulsion, thereby minimizing the loss of dissolved or suspended active ingredients carried in the initial or primary emulsion. As used in the specification and claims, the term "active ingredients" refer to materials which may be present in either phase of the primary emulsion but which do not substantially affect either the formation of the emulsions or the coacervation process.

The present process and products resulting therefrom afford a new approach to the provision of impermeable coatings of high strength or coatings which permit a gradual release of contents for water-soluble materials broadly, a problem which has heretofore resisted solution by the known techniques of coacervation. For example, encapsulated emulsion particles can be prepared containing active ingredients in the emulsion phases for use as sustained release fertilizers, plant growth hormones and pesticides such as fungicides, nematocides, bactericides and viricides for agricultural use. In addition, ingredients can be incorporated in pre-mixed foods which could not normally be included because of loss in the drying process, the encapsulated ingredients being liberated by the shearing force exerted in a mixing step prior to actual use. Similarly, vitamins, notably combinations of water-soluble and oil-soluble vitamins, can be incorporated into dry cereal preparations for release in the body. Cosmetics can be prepared in which the topical agent is enclosed by impermeable but readily destructible coacervate shells. Pharmaceutical materials can be encapsulated for sustained release in the body or for delayed release until the capsules are contacted with predetermined conditions, for example, a medium of predetermined pH or an enzyme system, or where stability, odour, taste or incompatibility problems are present. Such materials can be enclosed in coating suitable for oral, topical or injectable use by regulation of the particle size and coating thickness, permeability and hardness, or by selection of coating components. Insecticides with selective toxicity for inserts but which are relatively non-toxic toward humans can be encapsulated, for example, with coacervate coatings which are highly impermeable except in the presence of enzymes of the insects. Rodenticides which are effective on ingestion by the animals but which have odours that forewarn or repel them can likewise be coated by the method of this invention with virtually complete impermeability with respect to the odour.

The term hydrophilic liquid is intended to refer to water, aqueous solutions or suspensions, and non-aqueous solutions or suspensions immiscible in the oil phase of the primary emulsion.

In addition to emulsions containing soluble or suspendable active ingredients in the hydrophilic liquid phase of the primary emulsion, the coacervates obtained by practice of the present invention, can be deposited about any emulsion containing dissolved or suspended active ingredients in the oil phase of the primary emulsion. The ingredients to be dissolved or suspended in either the hydrophilic liquid or the oil phase, or both, of the primary emulsion are limited in selection only by the solubility, suspending characteristics or compatibility of the ingredients in both phases.

As employed herein, the term "primary emulsion" is intended to refer to the emulsion initially formed by the dispersion of the hydrophilic liquid, with or without dissolved or suspended active ingredients, in the selected oil, which may also contain dissolved or suspended active ingredients. The selection of the oil is not critical and is dependent on the function to be served by the oil, i.e., as a solvent or suspending medium or merely as the external phase of the primary emulsion. Thus, virtually any animal, vegetable, mineral or synthetic oil having the desired physical characteristics can be employed for this purpose. Lanolin, corn oil, soybean oil, castor oil, cod liver oil and mineral oil are examples of such oils.

The conventional emulsifying agents, such

as esters of polyhydric alcohols, sorbitan derivatives and polyoxyethylene derivatives, may be employed to facilitate and stabilize the said primary emulsion. The HLB (hydrophile-lipophile balance) system, described in Remington's Practice of Pharmacy, 11th edition, Mack Publishing Company, 1956, page 191, offers a convenient method for selection of the specific emulsifiers. Thus, by noting the HLB requirement for the particular emulsion system involved, an appropriate agent or combination of agents can be identified which will facilitate the formation and stabilization of the desired emulsion. As with all emulsion formation problems, selection of the most suitable agents must ultimately be based on trial. Accordingly, a sample of the final emulsion should be checked, for example, by diluting and agitating with a relatively large volume of water, to determine that a stable emulsion of the type desired has actually been obtained. Additionally, the selected agents must be compatible with the formation of a coacervate.

The thickening agents used herein in both the internal hydrophilic phase and in the coacervating solution are materials which are substantially insoluble in the oil phase of the primary emulsion and are capable of increasing the viscosity of the internal hydrophilic liquid or of the coacervating solution as hereinafter defined. Suitable agents for this purpose embrace the known natural and synthetic thickening agents, specifically including those alluded to in Thickening Agents Used in Pharmacy, by Charles H. Becker, American Professional Pharmacist 20:939 (October) 1054, such as acacia, tragacanth, methyl cellulose, carboxymethylcellulose and magnesium aluminum silicate, as well as other thickening agents such as the polyglycols, glycerin and syrups. The specific amounts of these materials may vary with the particular agent and system involved and can be readily determined by routine experimentation.

The coacervating solution which is emulsified with the mixture of the primary emulsion and the coacervating colloid preferably, but not necessarily, contains a thickening agent of the type described above. Such materials perform a role not fully understood, but their presence has been found to contribute substantially to the retention of dissolved or suspended ingredients in the respective phases of the primary emulsion during the process of coacervation.

The term "anti-inversion agent" as used herein is intended to refer to any material capable of preventing the invention of the capable of preventing the inversion of the to an oil-in-hydrophilic liquid emulsion on dispersion of the said primary emulsion in the coacervating solution to form the secondary emulsion. Although they may also serve as emulsifying agents, the anti-inversion agents are restricted to agents present in the oil-phase of the primary emulsion and it is frequently found advisable to have present both emulsifying agents and anti-inversion agents, and in some cases the same compound may be used for both purposes. Materials contemplated in the term anti-inversion agent include surface active agents, preferably those of the nonionic type, and known oil-thickening agents such as the natural and synthetic waxes, solid fats, sterols, and other conventional oil-gelling or oil-thickening agents. Examples of the said surface active agents include the sorbitan fatty acid esters and the polyoxyethylene sorbitan fatty acid esters. The oil-thickening agents include, for example, beeswax, carnauba wax, paraffin wax, saturated fatty acid esters, sitosterol, cholesterol, stigmasterol, and hydrogenated castor oil. In general, oil-thickening agents, including the oil-gelling agents, suitable for use as anti-inversion agents are those which are retained in the oil, i.e., agents having a higher heat of immersion in the hydrophilic liquid than in the oil. Specifically to be mentioned is the use of ethyl cellulose as an anti-inversion agent in such hydrocarbon systems as water-in-xylene or water-in-benzene emulsions, as well as water-in-chlorinated hydrocarbon systems. An ethyl cellulose film envelopes both the hydrocarbon and water phases of such emulsions and affords a suitable surface on the external phase on which to deposit a coacervate of the type herein described. An exceedingly stable emulsion can be prepared in this manner. No generalization can be made regarding the amount of oil-thickening agent required as the anti-inversion agent in any given emulsion system, as the amount will vary with the specific oil included therein; routine testing of the stability of the desired emulsion on dilution with water will indicate the necessary concentration.

The term "coacervating colloid" is intended to refer to a gelable hydrophilic colloid which, when in an aqueous sol (including solutions thereof) and on the addition of a coacervating agent, forms a liquid colloid-rich and a colloid-poor phase, the colloid-rich phase depositing about single or aggregated emulsion particles, the colloid-poor phase constituting the equilibrium liquid. Suitable gelable hydrophilic colloids include gelatin, agar-agar, albumen, alginates, casein, pectins, starch and fibrinogen, the preferred colloid being gelatin. The ultimate thickness of the coacervate enclosing the secondary emulsion particles will depend on the amount of colloid available for formation of the coacervate and the surface area of secondary emulsion particles to be encapsulated.

The term "coacervating agent" refers to

materials capable of initiating the separation of a colloid-rich phase and a colloid-poor phase from an original single phase colloidal sol (or solution). Such substances contemplated by the term coacervating agent include (1) aqueous solutions of electrolytes, including organic and inorganic salts, e.g., salts having alkali or alkali-metal cations such as sodium, ammonium, magnesium and potassium, and organic or inorganic anions such as sulphate, phosphate, acetate, formate, and (2) liquids which are water-soluble and in which the coacervating colloid is less soluble than in water. A critical concentration exists for each coacervating agent below which coacervation will not occur. This concentration must be determined for each combination of coacervating colloid and coacervating agent by routine testing.

The term "coacervating solution" applies to the mixture of the coacervating agent and the sol of the coacervating colloid, both as defined above, with or without a thickening agent, prior to the separation of the aforesaid colloid-rich phase (coacervate).

The term "secondary emulsion" refers to the emulsion formed when the primary emulsion is added to the coacervating solution before coacervation takes place. The secondary emulsion is in effect a double emulsion comprising the primary emulsion dispersed in the coacervating solution and exists as an entity only until a coacervate is formed about the particles of the secondary emulsion.

In the preferred embodiment of this invention, a primary water-in-oil emulsion is prepared by emulsifying (1) an aqueous solution containing the desired active ingredient, together with a small quantity of methyl cellulose as a thickening agent, into (2) approximately an equal volume of a vegetable oil such as corn oil containing a small amount of hydrogenated castor oil as the anti-inversion agent at a temperature of approximately 55° C. A gelatin sol and the primary emulsion are introduced as a single stream into a sodium sulfate solution (coacervating agent) containing acacia (thickening agent) under constant and vigorous stirring to produce the secondary emulsion, the temperature being maintained at approximately 55° C. throughout the period of mixing. Coacervation occurs rapidly on contact of the gelatin sol and the primary emulsion with the sodium sulphate, the secondary emulsion existing only momentarily in the coacervating solution. The temperature of the equilibrium liquid containing the coacervate is then reduced to 5° C. over a period of about 30 minutes to gel the coacervate. After adjusting the pH to the alkaline side, formaldehyde is added to the equilibrium liquid containing the new gelled coacervate to harden the coacervate, and the hardened coacervate is then filtered from the equilibrium liquid, washed and dried to give small particles of encapsulated emulsion.

In the preparation of the primary emulsion, the conventional emulsifying agents are normally employed, as previously indicated, to facilitate the establishment of and contribute to the stability of the primary emulsion, as well as to assure that the correct type of emulsion, i.e., hydrophilic liquid-in-oil, is obtained. Since the size of the final encapsulated emulsion particles depends in part on the size of the emulsion droplets of the primary emulsion, the degree of dispersion of the hydrophilic liquid in the oil should be regulated in accord with the desired particle size of the ultimately obtained coacervate.

The temperature at which the primary emulsion is prepared is of little consequence with respect to the functioning of the present process. However, it is necessary that the temperature at which coacervation is carried out be above the gel point of the coacervating colloid and within or closely approaching the gelling or thickening range of the thickening agent present in the hydrophilic liquid phase of the primary emulsion. Where methyl cellulose is employed as the thickening agent, this thickening range lies about 50° C. After the coacervate shell has enveloped the emulsion particles, the temperature is lowered below the gel point of the coacervating colloid. Where gelatin is employed as this component, reduction in the temperature to 30° C. or lower, depending on the type of gelatin used, preferably to about 5° C., will produce the desired gelation.

As indicated previously, the secondary emulsion exists during the interval between the first contact of all ingredients of the coacervating solution and the actual formation of the coacervate. The secondary emulsion is a double emulsion consisting of particles of the primary emulsion as the internal phase dispersed in the coacervating solution as the external phase. If the primary emulsion and the solution of the electrolyte are added to the aqueous solution of the coacervating colloid, the double or secondary emulsion will persist until the concentration of the coacervating agent reaches the necessary level at which coacervation will occur. Where, for example, sodium sulphate solution is employed as the electrolyte, the critical concentration with gelatin as the coacervating colloid has been found to be approximately 7%. However, where, as by the preferred sequence, the coacervating colloid and the primary emulsion are added together to the coacervating agent, a sufficient concentration of the coacervating agent is present at all times during the addition, and accordingly the secondary emulsion persists for only a short interval before coacervation

takes place. Where the coacervating agent is a solvent in which the colloid is less soluble than it is in water, the solvent is added slowly to a mixture of the primary emulsion and the coacervating colloid with constant stirring to form the secondary emulsion. When the critical concentration range is reached for the particular colloid and solvent involved, coacervation will occur. Throughout either of the above procedures, the temperature must be above the gel point of the coacervating colloid.

The ultimate particle size of the coacervate product is dependent in part, as heretofore indicated, on the degree of dispersion or size of the emulsion particles of the primary emulsion. In addition, the particle size is of course a function of the thickness of the coacervate coating. Also of importance in this regard is the degree of dispersion of the primary emulsion and coacervating colloid in the coacervating agent. The more complete and rapid the mixing, the smaller are the secondary emulsion droplets that are presented as nuclei about which the coacervate will form, and hence the smaller will be the final coacervate units.

The gelling step is significant with respect to the permeability of the coacervate membrane. With many coacervate systems, instantaneous gelling of the warm coacervate, as by adding the warm coacervate to ice water, produces a coacervate membrane having high permeability. A prolonged period of slow cooling also favours a membrane of high permeability. With many coacervate systems the lowest permeability (or highest impermeability) is obtained with intermediate cooling rates. Thus, a highly impermeable coacervate coating is produced in the case of a gelatin coacervate on cooling the newly-formed coacervate to about 5° C. in a period of approximately 30 minutes with continuous stirring.

Following gelation of the liquid coacervate, the gelled coacervate optionally can be hardened, plasticized or otherwise treated to adapt it to the intended use. Treating the gelled coacervate, for example, with a 37% aqueous solution of formaldehyde under alkaline conditions for about 1 hour produces a coacervate shell which can then be dried. Variations in the hardness of the coacervate shell can be obtained by varying the quantity of hardening agent and/or the period of contact therewith. Hardening likewise has considerable influence on the permeability of the coacervate, both with respect to the invasion of environmental fluids which would cause disintegration of the coating and to the containment of active ingredients which would otherwise impart undesirable odour or taste characteristics to the product.

The finally treated coacervate can be separated by centrifuging, filtering, decanting or the like. This can be followed by drying by known methods, as by spray drying, freeze drying, air drying, direct heating and the like, optionally preceded by a washing step, to obtain a product essentially free of surface moisture. Such a product can then be formulated as a dry material.

A convenient and informative test for the integrity of a coacervate coating produced by the method of the present invention involves the incorporation of a soluble dye in the hydrophilic liquid phase of the primary emulsion. The coacervate is formed in the manner described and the resulting material, after gelling and, optionally, after hardening, is dispersed or immersed in the test liquid. The liquid is gently stirred to thoroughly expose all coacervate surfaces. Any dye escaping from the hydrophilic liquid phase through the coacervate shell is readily detectable in the test liquid.

The following examples are illustrative of the process and products of the present invention but are not to be construed as limiting the scope of the invention.

Example 1

A water-in-oil emulsion is prepared by emulsifying at 40° C. 10 ml. of water in which is dissolved 20 gm. of urea into 25 ml. of corn oil containing 0.25 gm. of hydrogenated castor oil. A sol of gelatin as the coacervating colloid is prepared by adding 10 gm. of gelatin to 100 ml. of water and heating to 40° C. Twenty grams of sodium sulphate is dissolved in 80 ml. of water and this solution diluted to 100 ml. with water. The emulsion and gelatin sol are heated to 40° C. and charged slowly in a confluent stream into the sodium sulphate solution, also heated to 40° C., the latter being agitated vigorously throughout the period of addition to disperse the incoming stream as soon as possible after its introduction, whereby to form a double emulsion of the oil particles (containing dispersed urea solution) in the coacervating solution. Coacervation occurs rapidly, and on completion of the phase separation the temperature of the equilibrium liquid containing the coacervate-coated emulsion is lowered to 5° C. to gel the coacervate. Ten per cent sodium hydroxide solution is added to raise the pH to 9.5. Ten milliliters of formaldehyde solution is added to the resulting product to harden the coacervate shell, and the mixture is allowed to stand for 1 hour at 5° C. The hardened coacervate is then separated from the mixture by centrifugation, washed and spray dried at 80° C. (exhaust temperature).

The foregoing process is likewise operable with other anti-inversion agents substituted for the hydrogenated castor oil employed above, e.g., nonionic surface active agents

and hydrophobic oil-thickening agents such as the natural and synthetic waxes, solid fats, sterols and the like. Likewise, other oils can be selected as the external phase of the primary emulsion, and solutions or suspensions of other materials can be incorporated as the internal phase of the said emulsion. Instead of gelatin as the coacervating colloid, other gelable hydrophilic colloids including agar-agar, albumen, alginates, casein pectins, starch and fibrinogen can be used. In addition to the sodium sulphate employed above, other solutions of electrolytes such as potassium chloride and sodium acetate, or solvents such as alcohol and acetone, are suitable as coacervating agents.

The products of this example find application as a source of nitrogen for fertilisers for agricultural use in which a prolonged release is desired.

EXAMPLE 2

Following the procedure of Example 1 but substituting the same quantities of cod liver oil for the corn oil, lecithin for the hydrogenated castor oil, 3 gm of ascorbic acid for the urea and potassium chloride for the sodium sulphate, there is produced a coacervate which can be incorporated in dry cereals.

EXAMPLE 3

A water-in-oil emulsion is prepared by emulsifying at 50° C. 33 ml. of water containing 0.4 gm. of methyl cellulose into 33 ml. of mineral oil containing 0.33 gm. of sorbitan monooleate. A gelatin sol comprising 12.5 gm. of gelatin in 125 ml. of water is heated to 50° C., mixed with the emulsion, and added slowly to 125 ml. of a 20% ammonium phosphate solution, also heated to 50° C. The ammonium phosphate solution is vigorously stirred throughout the period of addition. The temperature of the mixture is lowered to 5° C. to gel the coacervate. Sufficient 10% sodium hydroxide solution is added to bring the pH to 9.5, followed by hardening of the coacervate with 12.5 ml. of 37% formaldehyde solution for 2 hours. The hardened coacervate is then filtered from the mixture washed and dried.

Instead of inducing coacervation with ammonium phosphate solution, absolute ethyl alcohol, heated to 50° C., can be added slowly to the mixture of the emulsion and gelatin sol with constant and vigorous mixing. Coacervation occurs when the coacervating concentration range is reached, a total of approximately 150 ml. of ethyl alcohol being required.

The above-formed coacervates are highly impermeable to acid and alkaline solutions, as indicated by the small amount of dye lost to test liquids on prolonged exposure thereto.

EXAMPLE 4

A water-in-oil emulsion is prepared by emulsifying at 40° C. into 37 gm. of lanolin containing 0.25 gm. of polyoxyethylene sorbitan monostearate, 30 ml. of water in which is dissolved 0.5 gm. of D. & C. Green No. 5. A gelatin sol comprising 15 gm. of gelatin in 150 ml. of water is heated to 40° C. and thoroughly mixed with the emulsion and the resulting mixture introduced slowly into 150 ml. of a 20% solution of sodium sulphate containing 25% of acacia previously heated to 40° C. During the period of addition, the sodium sulphate solution is vigorously stirred. The temperature of the resulting equilibrium liquid containing the coacervate-coated emulsion is reduced to 5° C. and 15 ml. of 37% formaldehyde solution added to harden the coacervate shell. After 2 hours, the coacervate is separated from the equilibrium liquid, washed and dried.

Substitution of 150 mg. of neomycin for the green dye above is productive of a coacervate which can be incorporated as dry, finely divided granules in topical compositions of the ointment type by the usual methods.

EXAMPLE 5

An ethyl alcohol-in-oil emulsion is prepared by emulsifying at 50° C. into 33 ml. of peanut oil containing 4 gm. of beeswax, 33 ml. of ethyl alcohol in which is dissolved 0.5 gm. of D. & C. Green No. 5 and 0.2 gm. of tragacanth. A fibrinogen sol is prepared at 50° C. from 12.5 gm. of fibrinogen and 125 ml. of water and is thoroughly mixed with the emulsion. The resulting mixture is added slowly to 125 ml. of a 20% barium chloride solution containing 37 gm. acacia, the barium chloride solution being vigorously agitated throughout the period of addition to facilitate coacervate formation. The temperature of the equilibrium liquid containing the coacervate-coated emulsion is lowered to 5° C. and 10% sodium hydroxide is added to give a pH of 9.5. Thereafter, 12.5 ml. of 37% formaldehyde is added to harden the coacervate shell. After standing for 5 hours, the resulting product is filtered from the mixture, washed and dried. Exposure of the above coacervate to acid and neutral test solutions indicates that a highly impermeable coating has been obtained which will release the capsule contents slowly over a prolonged period.

Substitution of 5 gm. of ethylene dibromide for the green dye above gives a nematocide which can be worked into the soil for effective long-term protection against worms and the like.

EXAMPLE 6

A glycerin-in-oil emulsion is prepared by emulsifying 75 ml. of glycerin at 50° C.

into 75 ml. of peanut oil containing 0.75 gm. of hydrogenated castor oil. A gelatin sol is prepared from 50 gm. of gelatin in 500 ml. of water heated to 50° C. The sol is mixed with the said emulsion and the resulting mixture added slowly to 500 ml. of a 20% sodium sulphate solution, also heated to 50° C. The sodium sulphate solution is vigorously stirred throughout the period of addition. The temperature of the mixture is then lowered to 5° C. to gel the coacervate. Sufficient 10% sodium hydroxide solution is then added to bring the pH to 9, and 50 ml. of 37% formaldehyde is introduced to harden the coacervate shell. After 4 hours, the hardened coacervate is then filtered from the mixture, washed and air dried at 80° C.

In addition to glycerin as the dispersed phase of the primary emulsion, as illustrated above, other nonaqueous solutions or suspensions immiscible in the oil phase can be used. Similarly, with such other emulsion systems other anti-inversion agents such as nonionic surface active agents and oil-thickening agents, e.g., natural and synthetic waxes, solid fats and sterols, can be substituted for hydrogenated castor oil employed above.

EXAMPLE 7

A water-in-oil emulsion is prepared by emulsifying at 40° C. 2 ml. of water into 20 ml. of soybean oil containing 0.2 gm. of magnesium aluminum silicate. A gelatin sol containing 10 gm. of gelatin in 90 ml. of water is thoroughly mixed with the said emulsion, heated to 40° C., and the resulting mixture added slowly, with continuous agitation, to 100 ml. of 98% methanol at 40° C. The temperature of the resulting equilibrium liquid containing the coacervate-coated emulsion is then reduced to 5° C. and 12 ml. of 37% formaldehyde solution added to harden the coacervate shell. After standing for 5 hours, the coacervate is separated from the equilibrium liquid, washed and dried.

Other anti-inversion agents can be substituted for the agent employed above, e.g., nonionic surface active agents and oil-thickening agents such as natural and synthetic waxes, solid fats and sterols. Also, other oils can be selected as the external phase of the primary emulsion, and nonaqueous coacervating agents other than methanol can be employed, the latter being those solvents in which the coacervating colloid (e.g., gelatin, as above, or other gelable hydrophilic colloids) is less than it is in water.

WHAT WE CLAIM IS:—

1. A process for coating particles of a hydrophilic liquid-in-oil emulsion which comprises forming a primary hydrophilic liquid-in-oil emulsion containing an anti-inversion agent in the oil phase and dispersing the primary emulsion in a coacervating solution comprising a coacervating agent as hereinbefore defined and an aqueous sol of a coacervating colloid as hereinbefore defined at a temperature above the gel point of the coacervating colloid to form a secondary emulsion, whereupon a coacervate is deposited about the particles of the secondary emulsion.

2. A process as claimed in Claim 1 wherein the hydrophilic liquid and/or the oil used in forming the primary hydrophilic liquid-in-oil emulsion contains dissolved or suspended active ingredients as hereinbefore specified.

3. A process as claimed in Claim 1 or 2 wherein the primary hydrophilic liquid-in-oil emulsion is formed by emulsifying the hydrophilic liquid and an animal, vegetable, mineral or synthetic oil in the presence of an emulsifying agent.

4. A process as claimed in any preceding claim in which the hydrophilic liquid phase of the primary emulsion contains a thickening agent.

5. A process as claimed in any preceding claim in which the coacervating solution contains a thickening agent.

6. A process as claimed in Claim 4 or 5 in which the thickening agent is methyl cellulose or acacia.

7. A process as claimed in any preceding claim in which the anti-inversion agent is a non-ionic surface active agent or an oil-thickening agent.

8. A process as claimed in Claim 7 in which the anti-inversion agent is hydrogenated castor oil, beeswax, or sorbitan monooleate.

9. A process as claimed in any preceding claim in which the coacervating agent is an electrolyte.

10. A process as claimed in any preceding claim in which the hydrophilic liquid of the primary emulsion is water.

11. A process as claimed in any preceding claim in which any coacervate deposited about the particles of the secondary emulsion is gelled by cooling and the coated particles are separated by centrifuging, filtering or decanting and are then subjected to spray drying, freeze drying, air drying or direct heating.

12. A process for coating particles of a water-in-oil emulsion which comprises preparing a primary water-in-oil emulsion by emulsifying an aqueous solution containing an active ingredient as hereinbefore specified together with methyl cellulose into about an equal volume of a vegetable oil containing hydrogenated castor oil, introducing the primary emulsion and a gelatin sol in a single stream into an agitated sodium sulphate solution containing acacia at a temperature maintained at about 55° C. throughout the period of mixing, reducing the temperature to

5° C. over a period of about 30 minutes to gel the coacervate, adjusting the pH to alkaline and adding formaldehyde to the equilibrium liquid containing the now gelled coacervate to harden the latter, and then filtering the coacervate from the equilibrium liquid and washing and drying to give small particles of encapsulated emulsion.

13. A process as claimed in Claim 12 wherein the vegetable oil used is corn oil and the primary emulsion is prepared at about 55° C. in the presence of an emulsifying agent.

14. A composition of matter which comprises a hydrophilic liquid-in-oil emulsion enclosed in a simple coacervate coating, the coacervating component of which is a gelable hydrophilic colloid.

15. A composition as claimed in Claim 14 in which there are dissolved or suspended in the emulsion active ingredients as hereinbefore specified.

16. A process for the preparation of an encapsulated hydrophilic liquid-in-oil emulsion substantially as herein described with reference to any of the examples.

17. An encapsulated hydrophilic liquid-in-oil emulsion when prepared by a process as claimed in any of Claims 1 to 13 or 16.

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